Pretreatment HIV Drug Resistance Increases Regimen Switch in Sub-Saharan Africa

9th Interest meeting, May 07 session 2
Harare Zimbabwe

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Background

• More people on ART: 90-90-90 targets
• Durability of first-line ART is important
  > Low availability of second-line ART

• Pretreatment drug resistance is on the rise in east and southern Africa *Gupta et al. Lancet 2012*

Impact of pretreatment drug resistance:

• 2-3x more risk of virological failure and acquired drug resistance after 1 year

Objective

What is the association between pretreatment drug resistance and long-term clinical outcomes on first-line ART?
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Outcomes

1. All-cause mortality
2. New AIDS events
3. Switch to second-line ART, due to presumed treatment failure.
4. Combined: poor outcome on first-line ART (1 t/m 3)
Methods:
Observational cohort study

6 countries, 13 clinical sites

Enrollment 2007-2009
- With and without on-site VL testing
- Standard first line NNRTI + 2NRTI
- Previous ARV exposure allowed

Monitoring of routine care:
2-3 years of follow up
Methods:
Observational cohort study

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Monitoring of routine care:
2-3 years of follow up

Study blood sample
Retrospective testing
- Genotyping at ART initiation
- VL at switch and genotyping if VL>1,000 cps/ml
Methods: definitions & analysis

Pretreatment drug resistance (PDR) =
Reduced susceptibility to ≥1 drug in regimen

Switch = switch to second-line (boostedPI + 2NRTI) ART due to presumed treatment failure; substitutions with PI's were censored

Unnecessary switch = switch with VL<1,000 cps/ml or VL>1,000 cps/ml & wild-type virus (determined retrospectively)

Time-to-event analysis for poor clinical outcomes
Cox model, adjusted for
  • Time-varying covariates: CD4 count, 30-day adherence (≤95% VAS)
Results: PASER-M cohort characteristics

N=2,579 initiated first-line NNRTI-based ART

Median age: 37 years [IQR 32-43]
Sex: 58% female
Prev. ARV exp.: 4.5% (no PDR 3.5%; PDR 20.6%)
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<table>
<thead>
<tr>
<th>Baseline genotyping</th>
<th>N=2,579</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type virus</td>
<td>2,222 (86.1%)</td>
</tr>
<tr>
<td>≥1 mutation, GSS = 3</td>
<td>216 (8.4%)</td>
</tr>
<tr>
<td>≥1 mutation, GSS &lt; 3</td>
<td>141 (5.5%)</td>
</tr>
<tr>
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<td>357 (13.8%)</td>
</tr>
<tr>
<td>NNRTI resistance</td>
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Baseline genotyping N=2,579

<table>
<thead>
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<th>HIV-1 subtype</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>53.4</td>
</tr>
<tr>
<td>A</td>
<td>17.6</td>
</tr>
<tr>
<td>CRF01_AE</td>
<td>8</td>
</tr>
<tr>
<td>CRF02_AG</td>
<td>5.6</td>
</tr>
<tr>
<td>D</td>
<td>10.7</td>
</tr>
<tr>
<td>B,F,G,J,K</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Wild-type virus 2,222 (86.1%)
≥1 mutation, GSS = 3 216 (8.4%)
≥1 mutation, GSS < 3 141 (5.5%)
≥1 mutation 357 (13.8%)
NNRTI resistance 297 (11.5%)
NRTI resistance 69 (2.7%)
Combined end point: poor outcome on first-line ART

- all-cause mortality
- and/or
- new AIDS event
- and/or
- switch to second-line

**adjusted HR 2.00**

95% CI: 1.17-3.42

p=0.011

PDR=Pretreatment drug resistance. Tarone-Ware test, p = 0.0001
1) All-cause mortality

- Early mortality
- 66.5% HIV-related mortality

**adjusted HR 0.75**

95% CI: 0.24-2.35
p=0.617

PDR=Pretreatment drug resistance. Tarone-Ware test, p = 0.5746
2) New AIDS events

Adjusted HR 1.06
95% CI: 0.68-1.64
p=0.807

Number on first-line ART(events):

<table>
<thead>
<tr>
<th></th>
<th>No PDR</th>
<th>PDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2337</td>
<td>131</td>
</tr>
<tr>
<td>90</td>
<td>(135)</td>
<td>(10)</td>
</tr>
<tr>
<td>365</td>
<td>1872</td>
<td>96</td>
</tr>
<tr>
<td>730</td>
<td>(29)</td>
<td>(0)</td>
</tr>
<tr>
<td>1096</td>
<td>1205</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>(8)</td>
<td>(0)</td>
</tr>
<tr>
<td>0</td>
<td>301</td>
<td>20</td>
</tr>
</tbody>
</table>

PDR=Pretreatment drug resistance. Tarone-Ware test, p = 0.7380
3) Switches to second-line ART, due to presumed treatment failure

Number on first-line ART switches:

<table>
<thead>
<tr>
<th>PDR</th>
<th>131 (4)</th>
<th>102 (14)</th>
<th>71 (4)</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PDR</td>
<td>2337 (14)</td>
<td>1964 (52)</td>
<td>1286 (15)</td>
<td>327</td>
</tr>
</tbody>
</table>

PDR=Pretreatment drug resistance. Tarone-Ware test, \( p < 0.0001 \)

**adjusted HR 3.80**

95% CI: 1.49-9.68

\( p=0.005 \)
Combined end point: poor outcome on first-line ART

all-cause mortality

HR 0.75 (95%CI: 0.24-2.35)

new AIDS event

HR 1.06 (95%CI: 0.68-1.64)

switch to second-line

HR 3.80 (95%CI: 1.49-9.68)
### Reason for switch to second-line: by clinician

<table>
<thead>
<tr>
<th>Type of treatment failure</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Immunological</td>
<td>3</td>
<td>2.8</td>
</tr>
<tr>
<td>Clinical &amp; immunological</td>
<td>19</td>
<td>17.9</td>
</tr>
<tr>
<td>Clinical, immunological &amp; virological</td>
<td>37</td>
<td>34.9</td>
</tr>
<tr>
<td>Clinical &amp; virological</td>
<td>27</td>
<td>25.5</td>
</tr>
<tr>
<td>Immunological &amp; virological</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>Virological</td>
<td>9</td>
<td>8.5</td>
</tr>
<tr>
<td>Not reported</td>
<td>8</td>
<td>7.6</td>
</tr>
</tbody>
</table>

21.7% clinical/immunological

70.8% viral load
Study sample:
Virological characteristics at time of switch

- 0% VL < 1,000 cps/ml, no DRM (wild type)
- 10% VL ≥ 1,000 cps/ml, with DRM
- 30% VL ≥ 1,000 cps/ml, unknown DRM
- 50% No data
- 24% of patients could have (re-)suppressed on first-line ART: unnecessary switches
Virological characteristics at time of switch (*retrospectively*)

- **VL < 1,000 cps/ml**
- **VL ≥ 1,000 cps/ml**
  - No DRM (wild type)
- **VL ≥ 1,000 cps/ml**, with DRM
- **VL ≥ 1,000 cps/ml**, unknown DRM
- No data

Sensitivity analysis: association PDR and appropriate switches

**HR 6.22** 95% CI 2.02-19.09 p=0.001
Conclusions & implications

Pretreatment drug resistance

- does not cause excess mortality or AIDS related events up to 3 years on first-line ART
- is strongly associated with switching to second-line ART

→ **PDR drives the need for second-line ART:**
  major programmatic implications in resource-limited settings
Conclusions & implications

Pretreatment drug resistance

• does not cause excess mortality or AIDS related events up to 3 years on first-line ART
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→ PDR drives the need for second-line ART:
  major programmatic implications in resource-limited settings

Viral load monitoring is needed to

• avoid unnecessary switches; retention on first-line ART
• timely detect therapy failure and switch to second-line ART
  → prevent new AIDS events and mortality
Acknowledgements

Special thanks to all study participants, study doctors, laboratory staff, study coordinators and data team

The PASER network
Maureen Wellington, Margaret Siwale, Mariette Botes, Cissy Kityo,
Sulaimon Akanmu, Kishor Mandaliya, Nicaise Ndembi, Kim Steegen

Al GHD Amsterdam & Kampala
Tobias Rinke de Wit, Kim Sigaloff, Raph Hamers, Sonia Boender,
Pascale Ondoa, Corry Manting, Cathy Nalubwama, Miriam Nakitto, Martin Omello

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